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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/642,660
Filing Date: August 22, 2000
Appellant(s): SCHNECK ET AL.

Lisa Hemmendinger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/6/2006 appealing from the Office action mailed 4/20/2006

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

US application 09/954166.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- Matsui et al. Proceedings of the National Academy of Sciences, USA; December 1994, 91(26): 12862-12866.

- Dal Porto et al. Proceedings of the National Academy of Sciences, USA; July 1993; 90(14):6671-6675.
- Chang et al. Proceedings of the National Academy of Sciences, USA; Novmber 1994; 91(24):11408-11412.
- Harris et al., WO 94/09131.
- Abbas *et al.* Cellular and Molecular Immunology, 3rd ed., W.B. Saunders Company, Philadelphia, 1997, pages 125-137.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 56, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth a molecular complex comprising four fusion proteins that associate to form a molecular complex, and therefore the written description in this case is not commensurate in scope to claims that read on a molecular complexes further

comprising antigenic peptide that are bound to said complexes. The following *written description* rejection is set forth herein.

The claims recite an "antigenic peptide" as part of the invention. The specification defines an "antigenic peptide" as any peptide capable of inducing an immune response (page 19 lines 14-15). However, there does not appear to be an adequate written description in the specification as-filed of the essential structural features of the antigenic peptides, and what core structure is required to performs the function of inducing an immune response. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice a representative number of molecular complexes that comprise the broad range of antigenic peptides claimed. Neither has Applicant provided a sufficient written description of any structure that may be correlated to the "antigenic peptide". An "antigenic peptide" encompasses *any* molecule with the activity of stimulating/inducing an immune response, of which

encompasses a vast number of possible peptides sequences of which the specification has not adequately disclosed, so as to be entitled to the broad genus of peptides claimed. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 103

Claims 28-31 and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsui et al (Proc. Natl. Acad. Sci., USA, 91(26)12862-12866, 20

December 1994) in view of Dal Porto et al (Proc. Natl. Acad. Sci., USA, 90(14):6671-6675, 15 July 1993, previously cited) and Chang et al (Proc. Natl. Acad. Sci., USA, 91(24):11408-11412, 22 November 1994previously cited) and Harris et al (WO 94/09131, 4/28/1994).

Claims are drawn to a cellular composition comprising a molecular complex bound to the surface of the cell, wherein the molecular complex comprises a first and a second fusion protein, wherein said first fusion protein comprises an immunoglobulin heavy chain variable region (IgG1) and the extracellular domain of an MHC class IIβ chain or TCRα chain (extracellular domain of a first transmembrane polypeptide), wherein said heavy chain variable region and said MHC class IIβ chain or TCRα chain are connected by a first peptide linker, and said second fusion protein comprising an immunoglobulin light chain (Igk) and the extracellular domain of an MHC class IIα chain or TCRβ chain (extracellular domain of a second transmembrane polypeptide), wherein said immunoglobulin light chain (Igk) and said MHC class IIα chain or TCRβ chain are connected by a second peptide linker, whereby two first and two second fusion proteins associate to form a first molecular complex comprising at least four fusion proteins, comprising two ligand binding sites (i.e., divalent), each ligand binding site formed by the extracellular domain of the first and second transmembrane polypeptides (i.e., MHCIIα-MHCIIβ and TCRα-TCRβ), wherein the first molecular complex (divalent) has increased affinity for its ligand relative to a second molecular complex consisting of the extracellular domain of a first transmembrane polypeptide and the extracellular domain of the second transmembrane polypeptide (i.e., monovalent).

a. Matsui *et al* teach that despite the availability of monovalent forms of TCRs and MHC heterodimers, the interaction between these two molecules has been difficult to study directly due to the very low affinity (see abstract). Matsui *et al* teach that the interaction between monovalent TCR and MHC (class II MHC molecule I-E^k) heterodimers is a low affinity interaction, characterized by a slow association rate and a fast dissociation rate (see page12862, right column and Table 1 and Figure 2). Matsui *et al* do not specifically teach a method of making divalent TCR/IgG and class II MHC/IgG molecules, wherein both immunoglobulin heavy and light chains are linked at their N-termini to the extracellular binding domains of the TCR or class II MHC molecule. This deficiency is made up for in the teachings of Dal Porto *et al* and Chang *et al* and Harris *et al*.

b. Dal Porto *et al* teach a method for producing divalent high-affinity class I MHC/IgG molecules for studying cell-cell interactions and Dal Porto *et al* suggests that divalent MHC/IgG molecules are good candidates for high-affinity MHC-like molecules that could be used to selectively suppress specific T cell responses (see pages 6672 and 6675 and Figure 1B). Dal Porto *et al* teach divalent class I MHC/IgG molecules (H-$2K^b$/IgG) that demonstrate nanomolar affinities for T cell receptors and nanomolar concentrations of the divalent H-$2K^b$/IgG molecule specifically inhibited lysis of target cells by alloreactive H-$2K^b$-specific T cells, whereas monovalent H-$2K^b$ never inhibited the response of alloreactive H-$2K^b$-specific T cells to cells expressing native H-$2K^b$ molecules and previous indirect measurements of the interaction between monovalent MHC

class I and T cells suggests affinities in the micromolar range (see abstract and pages 6674-6675).

c. Chang *et al* teach that the generation of TCR molecules is hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and Chang teaches that fusion of peptide sequences known to form unique heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation (see entire document, particularly abstract, pages 11408, 11410-11411 and Figs. 2A and 3A).

d. Harris *et al* teaches methods for producing bivalent (i.e., divalent) binding proteins comprising fusing binding domains via a linker to the N-terminus of the variable regions of the heavy chain and the light chain and the fusion proteins retain binding activity and the binding domains can include cell surface receptors (see entire document, particularly pages 6-8, page 12, lines 15-19 and page 13, lines 7-16 and Figures 2, 6, 8 and 9). Harris *et al* teach that the genes encoding the fusion proteins can be expressed from one vector or from two different vectors (see page 29, lines 7-13).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al*.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al* because Matsui *et al* teach that the interaction between monovalent forms of TCRs and MHC heterodimers has been difficult to study directly, due to the very low affinity between these molecules and Dal Porto *et al* teach a divalent class I MHC/IgG molecule (H-2K^b/IgG) having nanomolar affinity for T cell receptors and nanomolar concentrations of the divalent H-2K^b/IgG molecule specifically inhibited lysis of target cells by alloreactive H-2K^b-specific T cells, whereas monovalent H-2K^b never inhibited the response of alloreactive H-2K^b-specific T cells to cells expressing native H-2K^b molecules and the interaction between monovalent MHC class I and T cells suggests affinities in the micromolar range. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method for making high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al* because Chang *et al* teach the generation of TCR molecules is hampered by inefficient pairing of α and β subunits in the absence their respective transmembrane regions and Chang teaches that fusion of peptide sequences known to form unique heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular

segments promotes heterodimer formation over homodimer formation and according to Chang this approach makes it possible facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II α and β subunits (see page 11412, right column) and Harris *et al* teach that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins. Therefore, the ordinary skilled artisan would have been motivated at the time the invention was made to express one TCR/MHC class II extracellular binding domain as a fusion protein with the immunoglobulin heavy chain and express the other TCR/MHC class II extracellular binding domain as a fusion protein with the immunoglobulin light chain in order to facilitate pairing and proper folding of the α and β polypeptides of the TCR and MHC class II molecules and one of ordinary skill in the art would have had a reasonable expectation of success because Harris demonstrates that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins. Further, one of ordinary skill in the art at the time the invention was made would have been motivated to have produced high affinity divalent TCR/IgG and class II MHC/IgG molecules to overcome the intrinsic low affinity of TCR and MHC heterodimers (monovalent), which has limited their use. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for

studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al*.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

(10) Response to Argument

I. The specification fully describes claims 32 and 56-58

A. Legal standards.

At pages 4-5 of the Brief, Appellant reviews the legal standard for 35 USC§ 112, 1st paragraph, which the examiner takes no issue.

B. The specification satisfies the legal requirements for a written description of claims 32 and 56-58 for at least two reasons.

Beginning at page 5, Appellant reviews the claims and presents Examiner's rejections maintained in the Office actions and indicates that the Examiner's position of written description is legally incorrect for two reasons

At pages 6-7, Appellant presents two main reasons for the Examiner's improper rejection. First, Appellant argues that the "antigenic peptides are neither new nor unconventional in the art and therefore do not require explicit description to those of skill in the art. Appellant points to several prior art reference which generally teach antigenic peptides and concludes that those of skill in the art would find the term conventional and fully described in the art. Appellant indicates that it need not be described in the specification. In response to Appellant's arguments, the written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, the broad class of "antigenic" peptides claimed is well known in the art to be a highly divergent class of peptides, because just about any peptide sequence to some extent is considered "antigenic". Because the specification has not provided a representative number of species in a highly divergent genus so that it can be used to encompass the broad scope of the peptides claimed, the written description for antigenic peptides has not been meet.

Second, Appellant argues that explicit description of individual species is not the only means of disclosing possession of a broad genus. Appellant cites the Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (January 5, 2001). Appellant further argues with regard to antigenic peptides, that there is a known correlation between structure and function and points to binding characteristics and binding profile in MHC class II molecules or T-cell receptors ("TCR").

In response to Appellants arguments, in deciding *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997), the Federal Circuit held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of "antigenic peptides" by only their common ability bind to the peptide binding site of an MHC or to the peptide binding site of a T-cell receptor TCR, does not serve to adequately describe the genus as whole. The Court indicated that while appellants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members. In this case, appellant has not specifically disclosed any particular structure or correlated any structure with any particular function, because the binding of the peptides to the MHC or TCR is not a function of the peptide per se, but rather a characteristics of the peptide. Moreover, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004). In this instance, as in that, there is no language that adequately describes with the requisite degree of particularity necessary to satisfy the written description requirement the of the genus of structurally variable polypeptides encompassed by the claimed "antigenic peptides". Again, a description of what a material does, rather than of what it is, does not suffice to describe the claimed invention. It is also aptly noted that with regard to the binding of an antigen to the TCRs, the antigenic peptide itself is incapable of binding to the TCRs in the absence of presentation by the MHCs. Therefore, the function ascribed to the "antigenic peptide" does not adequately define the genus as so claimed.

C. None of the case law the Examiner cites applies to the written description of the recited antigenic peptides

At pages 7-8, Appellant indicates that the Examiner has improperly cited case law to support his assertions and has incorrectly done so. In response to Appellants arguments, the examiner will not comment of the correctness of the cited case law and will defer to the Board of Patent of Patent Appeals and Interferences.

For the above reasons, it is believed that the rejection under 35 USC § 112, 1st paragraph should be sustained.

II. *Claims 28-32 and 51-55 are not prima facie obvious.*

A. Legal Standard.

At pages 9-10 of the Brief, Appellant reviews the legal standards for obviousness under 35 U.S.C. § 103(a), with which the Examiner takes no issue.

B. The rejection.

At pages 10-11 of the Brief, Appellant reviews the rejection. It should be noted that the teachings of Matsui are directed to the interaction between soluble forms of the T cell receptor (TCR) and class II MHC molecules (i.e., class II MHC molecule I-E^k), which Matsui characterizes as a low affinity interaction.

C. The examiner did not evaluate the cited references under the proper legal standard.

Beginning at pg. 11 of the Brief, Appellant reviews the scope and content of the prior art, reviewing the specific teachings of the cited references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

D. The combination of cited reference does not teach or suggest all elements of the claims subject matter.

Beginning at pg. 15 of the Brief Appellant argues that the combination of references cited by the examiner does not teach or suggest all of the elements of the claimed invention and one of ordinary skill in the art would have had no motivation to

select the isolated elements of the cited references and modify and combine them as the examiner asserts. Appellant argues that the teachings of Matsui et al would not have motivated one of ordinary skill in the art to make soluble divalent TCR/IgG and class II MHC/IgG molecules with higher binding affinities because although Matsui acknowledges the low affinity interaction between soluble TCRs and soluble peptide/MHC class II molecules, Matsui uses surface plasmon resonance to solve the problem of measuring the intrinsically low affinity interaction bewteen these molecules (Brief at pg. 12-13 and 16). Thus, Appellant argues that Matsui provides no motivation to make soluble TCR and class II MHC molecules with higher binding affinities and Chang teaches no other method of associating polypeptides other than by using leucine zipper components and Chang's teachings of leucine zippers would not have motivated an ordianary skilled artisan to use immunoglobulin chains (Brief at pg. 18). This has been fully considered but is not found persuasive.

The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (*Ruiz*, at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (*National Steel Car v. Canadian Pacific Railway Ltd.*, 357 F.3d 1319, 1338, 69 USPQ2d

1641, 1656 (Fed. Cir. 2004)). "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). In this case, the alleged solution provided by Matsui does not actually solve the intrinsically low affinity interaction between soluble MHC class II molecules and TCR heterodimers and would be of little practical use, such as inhibiting the lysis of target cells by alloreactive MHC-specific T cells in the treatment of transplant rejection, which require a high affinity interaction between MHC heterodimers and TCRs as taught by Dal Porto. Matsui merely provides an alternative for directly measuring the intrinsically low affinity interaction between soluble MHC and TCR heterodimers. The teachings of Dal Porto et al indicate that genetically engineered divalent MHC/IgG molecules have increased affinity for TCRs relative to the interaction between monovalent MHC molecules and TCRs on T cells (i.e., nanomolar verses micromolar affinity) and soluble divalent MHC (H-2K^b)/IgG molecules specifically inhibited lysis of target cells by alloreactive H-2K^b-specific T cells, whereas soluble monovalent MHC (H-2K^b) never inhibited the response of alloreactive H-2K^b-specific T cells to cells expressing native H-2K^b (see pp. 6674-6675). Further, in view of the teachings of Chang et al indicating that the generation of soluble TCR molecules is hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and the fusion of self-associating polypeptides to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over

homodimer formation, making it possible to facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II α and β subunits, providing a strong suggestion to one of ordinary skill in the art to modify Dal Porto's soluble divalent class I MHC/IgG molecular complex by fusing both TCR α and β extracellular segments or both MHC class II β and α extracellular segments to the N-terminus of the antibody heavy and light chains, respectively, to facilitate heterodimer formation. Thus, there would have been an advantage to producing soluble divalent class II MHC/IgG and TCR/IgG molecular complexes for inhibiting the lysis of target cells by alloreactive MHC-specific T cells in the treatment of transplant rejection, which is not possible using the low affinity soluble monovalent MHC class II and TCR molecules of Matsui and there would have been an advantage to fusing both TCR α and β extracellular segments or both MHC class II β and α extracellular segments to the N-terminus of the antibody heavy and light chains, respectively, to promote the heterodimer formation over homodimer formation in the absence of their respective transmembrane domains. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

The examiner acknowledges Appellants' criticism of Chang as not teaching anything other than leucine zippers, however, "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of

the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also In re Sneed, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures."). Additionally, Appellants criticism and remarks with respect to *In re Bozek* at pg. 8 of the Brief are acknowledged, however, the examiner is properly relying on the evidence in the prior art references themselves, and the motivation to combine made explicit therein as discussed supra.

At pg. 17 of the Brief, Appellant argues the art of Dal Porto stating that Dal Porto teach a molecule that differs substantially from the recited molecular complex. Appellant points out that the key difference is that the instantly recited molecular complexes comprise two different fusion proteins (Fig 1B "specification" at pg. 16 of the Brief) and modifying Dal Porto's molecule (Fig 1B "Dal Porto" at pg. 16 of the Brief) to arrive at the present molecular complex would have involved two modifications: (1) fusing the extracellular domain of a first transmembrane polypeptide to the immunoglobulin heavy chain in place of the class I MHC α chain of Dal Porto and (2) fusing the extracellular domain of a second transmembrane polypeptide to the immunoglobulin's light chain, not taught by Dal Porto. Further, Appellant notes that the fusion proteins of the recited molecular complex are not held together with lecine

zippers as taught in Chang (pg. 17 of the Brief). This has been fully considered but is not found persuasive.

As noted by Appellant, the presently claimed molecular complexes differ from the molecular complex of Dal Porto by substitution of the extracellular domains (α and β subunits) of the TCR or class II MHC molecules in place of the class I MHC portion of the molecule of Dal Porto and include one additional linkage to the immunoglobulin light chain. Thus, the presently claimed molecular complexes are not substantially different from the molecular complex of Dal Porto. It is reiterated that one of ordinary skill in the art would have been motivated to modify Dal Porto's soluble divalent class I MHC/IgG molecular complex by fusing the C-terminus of both TCR α and β extracellular segments or the C-terminus of both class II MHC β and α extracellular segments to the N-terminus of the antibody heavy and light chains, respectively, to facilitate heterodimer formation in view of the teachings of Chang, which indicate that the generation of soluble TCR molecules is hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and the fusion of self-associating polypeptides to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation, making it possible to facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II α and β subunits.

In addition, one of ordinary skill in the art would have had a reasonble expectation of success in making the above modification because Harris et al provides evidence that binding domains, including cell surface receptors or binding regions of

natural dimeric proteins can be fused via a linker to the N-terminus of the heavy and light chain variable regions without altering the binding function of the fusion proteins (see pp. 6-8 and 13 and Figs. 2, 6, 8 and 9). In contrast to Appellants arguments that Harris et al teach away from using immunoglobulin heavy and light chains, Harris et al teach that the association of heavy and light chains (Ka $>10^{10}$ M^{-1}) is derived from the combination of relatively weak V_H-V_L (Ka $\sim10^6$ M^{-1}) and C_H1-C_L (Ka $\sim10^7$ M^{-1}) interactions, indicating that the association of the two domain pairs is at least additive (Harris et al at pg. 11, lines 4-13), suggesting to one of ordinary skill in the art at the time the invention was made that using the naturally associating immunoglobulin heavy and light chains as taught by Dal Porto would provide greater stability. Thus, there would have been an advantage to using the immunoglobulin heavy and light chains in producing soluble divalent class II MHC/IgG and TCR/IgG molecular complexes for inhibiting the lysis of target cells by alloreactive MHC-specific T cells in the treatment of transplant rejection.

E. One of ordianry skill in the art would have had no motivation to select isoalted elements of the cited references, modify them, and combine then as the Examiner asserts

Appellant reiterates their arguments in the response filed February 10, 2005 that those of skill in the art at the April 28, 1996 priorty date of this application knew that no particular manipulation was needed to cause the extracellular domains of MHC class II molecules or TCRs to associate to form functional binding sites. Appellant states that it was well known that the two extracellular domains of TCR molecules or of class II MHC

molecules will associate to form a peptide binding site in the absence of their transmembrane domains, citing US Patent 5,732,309 (Table 2); US Patent 5,583,031 (Table 3); and pages 17-18 of the response filed February 10, 2005. Thus, even if, *arguendo*, one of ordinary skill had been motivated to modify Dal Porto's molecule to produce those claimed, the modification would have been to substitute one of the TCR or class II MHC extracellular domains for the MHC class I α chain in the fusion protein of Dal Porto, to express the other extracellular domain by itself, and to permit the two extracellular domains to associate as the prior art taught they would. This has been fully considered but is not found persuasive.

Again, while possible, Chang et al indicate that expression of the two extracellular domains of TCR or class II MHC molecules in the absence of their transmembrane domains results in the inefficient pairing bewteen α and β subunits, as monomers as well as homodimers, in addition to the desired heterodimers are produced (see bridging pargraph at pg. 11408). Chang teaches that fusion of self-associating polypeptides to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation, making it possible to facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II α and β subunits, providing explicit motivation to modify the soluble divalent class I MHC/IgG molecule of Dal Porto by fusing both MHC class II α and β extracellular segments or fusing both TCR α and β extracellular segments via a peptide linker to the heavy and light chains to efficiently pair the α and β extracellular segments in the absence of their respective transmembrane regions, thereby promoting heterodimer

formation. Thus, there would have been an advantage to fusing both MHC class II α and β extracellular segments or both TCR α and β extracellular segments via a peptide linker to the N-terminus of the self-associating heavy and light chain variable regions of the antibody of Dal Porto.

It is reiterated that "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also In re Sneed, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures.").

For the above reasons, it is believed that the rejection under 35 USC § 103(a) should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

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